08/459,141

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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
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EXAMINER: SMITH, L

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 5/3/96.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), ~~or thirty days, whichever is longer~~, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 10-23 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 10-23 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

– SEE OFFICE ACTION ON THE FOLLOWING PAGES –

* U.S. GPO: 1996-410-238/40050

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. The examiner acknowledges receipt of the amendment cancelling claims 1-9, adding claims 20-23 and amending the remaining claims. Claims pending and under consideration are claims 10-23.

3. The objection to the disclosure because of informalities is withdrawn in view of applicant's amendments. However, the amendment to page 25, line 26 was not made because in vitro does no appear and the amendment to page 24, line 17 was not made because Bglll does not appear.

4. The objection to claims 5, 6 and 18 under 37 CFR 1.75(c) in view of the cancellation of claims 5 and 6 and amendment to claim 18.

5. The provisional rejection of claims 1-19 under 35 U.S.C. §101 as claiming the same invention as that of claims 1-19 of copending application serial number 08/470,107 and claims 1-19 of copending application serial number 08/459,147 is withdrawn in view of applicant's cancellation of claims 1-9 and amendments to claims 10-19.

6. The rejection of claims 1-19 under 35 U.S.C. §112 second paragraph as failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention

is withdrawn in view of applicant's amendments and cancellation of claims 1-9.

7. The rejection of claims 1-6, 10, 14-17 under 35 U.S.C. §102 (b) as anticipated by Berman et al is withdrawn in view of applicant's cancellation of claims 1-9 and amendments to the remaining claims.

Applicant's arguments filed 5/3/96 have been fully considered but they are not deemed to be persuasive.

8. The rejection of claims 11, 13, 18 and 19 and newly presented claims 20-23 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 10, 13, 14, 17, 20-23 of copending application serial number 08/357,084 is maintained essentially for reasons set forth in paper no. 4, paragraph 19 of the previous office action. The examiner notes applicant's remarks with respect to this provisional ground of rejection.

9. The rejection of claims 10, 12, 14-17 and newly presented claims 13, 20-23 under 35 U.S.C. §112 first paragraph as the disclosure is enabling only for claims limited to a vaccine comprising a truncated, membrane free glycoprotein D polypeptide of herpes simplex virus and a method of producing the vaccine is maintained essentially for reasons set forth in paper no.4, paragraph 21 of the previous office action.

The rejection was on the grounds that The claims are very broadly drawn to a vaccine comprising membrane-bound and

membrane-free polypeptides from a pathogen capable of raising neutralizing antibodies to any pathogen. The examiner views the broad claims as encompassing all bacterial, viral, fungal and protozoan species. The specification lacks sufficient guidance and teaching to enable the entire scope of the claims. Moreover, the specification lacks sufficient guidance and teaching to enable the use of the glycoprotein C from herpes simplex virus. Indeed the specification states on page 46 that the function of the glycoprotein C is unknown and that it is not clear that gC is indispensable to the viruses during in vivo infection of the human and the establishment of latency. While the specification describes sequence homologies between gC and gF, the specification lacks enablement to show a correlation between gC and gD, such that one might reasonably expect similarity in structure and function. Thus it would appear that the role of the gC glycoprotein in generating protective immune responses has also not been clearly defined and one would not be able to reasonably predict success with a vaccine against herpes simplex virus comprising the glycoprotein C absence evidence of its function. In view of all of the above, it is determined that the specification is not commensurate in scope with the claimed subject matter.

Applicant urges that the mere fact that glycoprotein C has no known actual function is irrelevant as to whether or not it may act as an effective vaccine, all that is required for glycoprotein C to be effective as a vaccine is that it assists in eliciting neutralizing antibodies, page 5, lines 5-11 state that other classes of glycoproteins may be components of vaccines such as gC and that it is believed that a vaccine containing gD and gC glycoproteins would be more effective.

It is the examiner's position that the specification shows (pages 2-34) cloning and sequencing of the gD genes, expression of the gD glycoprotein, immunization of mice with gD glycoprotein (truncated and full length), and challenge with HSV. The specification also shows (pages 34-47 and example 2) cloning and

sequencing of the gC genes, expression of the gC glycoprotein and analysis of the amino acid sequence and the homology and similarity between gC and gF. The specification lacks enablement for a vaccine comprising gC and gD glycoproteins which would protect against HSV-1 and HSV-2 infections and would be more effective than either glycoprotein alone as stated in the specification. Moreover, there is no enablement for a vaccine such as gB or gA or gE. There is no guidance and teaching to show which dosages of the vaccine containing the mixtures would be effective in protection against HSV.

Applicant urges (further in the amendment, page 19) that "the provision of an absolute protective effect upon challenge, which is the hallmark, indeed the necessity, of a vaccine that could expect to be ultimately commercially successful" and that challenge data is necessary in order to prove the effectiveness of a vaccine.

It is the examiner's position that the instant specification provides challenge data to show the effectiveness of the gD glycoprotein against HSV-1 and HSV-2 infection. The specification provides no enablement to show that the gC glycoprotein was administered to animal models and challenged with HSV to show the effectiveness of the gC glycoprotein. Additionally, the specification lacks enablement for a mixture of glycoproteins such as gB and gD or gB and gC or any other

combination of proteins formulated into a vaccine and injected into animals. Adapting applicant's reasoning, it would appear that this is necessary for a vaccine composition. Therefore, in view of all of the above, it is determined that the specification is not commensurate in scope with the claimed subject matter.

10. Concerning the claim for priority, applicant urges that the instant specification contains an identical disclosure as the parent applications, therefore benefit of priority should be granted.

It is the examiner's position that the specification is not enabling for the entire scope of the claimed subject matter in that there is no enablement for a vaccine containing a mixture of glycoproteins. Applicant has not pointed to where in the specification there is enablement for a mixture of glycoproteins where the mixture containing, for example, gB and gD glycoproteins or any other mixture.

11. The rejection of claims 10, 11, 13-15, 18 and 19 under 35 U.S.C. 103 as being unpatentable over Watson et al, 1982 in view of Rose, 1982 is maintained essentially for reasons set forth in paper no. 4, paragraph 25 of the previous office action.

The rejection was on the grounds that the claims are drawn to a vaccine comprising a herpes simplex membrane-bound and truncated glycoprotein D expressed in a continuous mammalian cell culture, which vaccine is capable of raising neutralizing antibodies and methods of producing the vaccine. The examiner is viewing the term vaccine as an intended use since it appears to impart no other distinguishing characteristics to the gD glycoprotein of herpes simplex virus.

Watson et al teach the cloning and expression of the gene coding for herpes simplex virus type 1 glycoprotein D. The glycoprotein D is capable of generating antiserum which can neutralize infectivity of herpes simplex virus (HSV) type 1 and type 2. In vivo antiserum generated to the glycoprotein D protected mice from neurological disease induced by either HSV type 1 or type 2 (page 381). This was suggested to show "the potential for inducing immunity to infections of both HSV types with the use of a subunit vaccine consisting of a purified HSV-1 gD glycoprotein". The gD glycoprotein appears to be similar to the claimed membrane bound polypeptide. Also taught is the amino acid sequence of the gD glycoprotein (figure 2) including the signal sequence of the gD glycoprotein and the putative transmembrane region which appears around amino acid position 340 (page 382). It is stated that the signal sequence may be removed during translation (page 382). Watson et al also teach the construction of a glycoprotein D expression plasmid which appeared to have deleted 52 NH2-terminal amino acids from the gD glycoprotein (page 383, first column). Thus while Watson et al appear to describe a truncated gD glycoprotein, they differ from the claimed invention in not specifically describing a truncated secreted protein. However, Rose et al teach the expression of cell-surface secreted form of the vesicular stomatitis virus G protein which appears to be the model for integral plasma-membrane proteins (page 753). The G protein has the characteristic transmembrane domain and cytoplasmic domain and the truncated form of the G protein lacked these domains (page 754, second column). Expression of the truncated polypeptide did result in secretion of the polypeptide into the medium, although the rate was somewhat slow (page 758). However, the claims are not drawn to the rate of transport of the polypeptide. Thus it would have been obvious to one of ordinary skill in the art at the time the invention was made to express the glycoprotein D molecule either as a membrane glycoprotein or as a secreted glycoprotein (for ease in recovery from the cell culture medium) in a vaccine composition. It would have been expected, barring evidence to the contrary, that the glycoprotein D, either membrane bound or secreted, would be effective in a vaccine composition in generating neutralizing antibody responses, when administered. Additionally, given the sequence of the HSV glycoprotein D as depicted by Watson showing the transmembrane sequence and the suggestion by Rose of deleting the signal sequence as well as the transmembrane domain, one would have a reasonable expectation of success in generating a truncated glycoprotein wherein the first NH2-terminal 300 amino acids are present.

Applicant urges that Watson et al only expressed fusion proteins which contain other sequences and Watson et al do not express complete, intact and unassociated gD.

It is the examiner's position that the claims are drawn to a vaccine comprising the truncated, membrane free derivative. The claims are not drawn to an intact glycoprotein but a truncated glycoprotein. Watson et al describe a glycoprotein lacking coding regions for 52 amino acids. The glycoprotein appears to be "unassociated" particularly with the intact virus. Moreover,

Applicant's use of the open-ended term "comprising" in the claims fails to exclude unrecited steps and leaves the claims open for inclusion of unspecified ingredients, even in major amounts. See In re Horvitz, 168 F 2d 522, 78 U.S.P.Q. 79 (C.C.P.A. 1948) and Ex parte Davis et al., 80 U.S.P.Q. 448 (PTO d. App. 1948).

Applicant urges that Watson et al merely make reference to the capability of glycoprotein D in generating neutralizing antiserum which can neutralize infectivity and this is not actually the work of Watson et al.

It is the examiner's position that it appears then that it is well known in the art that antiserum generated to HSV glycoproteins can neutralize infectivity. Therefore, it would have been obvious, given what was well known in the art to include glycoprotein D in a vaccine composition and it would have

been expected that the glycoprotein D would generate neutralizing antibodies which would neutralize infectivity of HSV.

Applicant urges that Watson et al do not demonstrate that antiserum produced in vivo is capable of neutralizing HSV infectivity in vivo, a detailed reading of the reference indicates that monoclonal antibodies directed against the gD protein were obtained and were transferred to mice and that no antiserum was produced and tested.

It is the examiner's position that initially, the rejection is under 35 U.S.C. §103 over a combination of references not under 35 U.S.C. §102. It appears from Watson et al and from the instant arguments, that is well known in the art that antiserum generated to gD of herpes simplex virus can neutralize infectivity. Applicant appears not to dispute this. The generation of specific monoclonal antibodies is well known in the art. Generally, animals are immunized with an antigen, antiserum collected to determine the presence of specific antibodies and antibody producing cells from the immunized animal are fused with immortal cell lines to generate monoclonal antibodies. This enables the production of predefined specific monoclonal antibody. Again, the claims do not specify monoclonal or polyclonal antibody, just the capability of generating neutralizing antibody, which applicant would agree appears to be possessed by gD specific antiserum or a gD specific monoclonal antibody.

Concerning the Watson patents referred to by applicant, it should be noted that the issue is not whether or not substantial subject matter was introduced because a knowledge of the prosecution history of the Watson patents is not possessed by the examiner. The Watson patents are not under re-examination.

Applicant urges (in the instant response and similarly in responses in the parent application) that the Watson et al reference should include a review of the '694 and '315 patents issued to Watson because these documents show that protection achieved was at best between 30% and 80%, the present invention provides 100% protection against challenge with herpes simplex virus and this was unexpected. It is the examiner's position that while the '315 and '694 patents were not used in the rejections of record, table 4 of the '315 patent (to which applicant directs our attention) shows 100% protection against HSV-2 infection using glycoprotein D-1. Again, the claims are drawn to a vaccine effective against HSV. It would appear that the glycoproteins disclosed in the '315 patent appeared to be "effective" against HSV and in one case was 100% effective. Thus one would reasonably expect 100% effectiveness with glycoprotein D. Additionally, one would reasonably expect the recombinant glycoprotein D to function similarly.

Applicant urges that the specification does not lack support for the claim that the results of the vaccinated group were

unexpected and points to tables 1 and 2, pages 28 and 31 of the instant specification.

It is the examiner's position that tables 1 and 2 show that the control mice survived and that the untreated mice did not survive. This is not an unexpected result. One would reasonably expect mice immunized to survive a challenge moreso than unimmunized mice to survive a challenge. Indeed the '315 patent shows that unimmunized mice or mice immunized with an irrelevant antigen did not survive and HSV challenge. Again this is an expected result.

Applicant urges that Rose et al provide support for applicant's contention that the truncated material of the present invention provides unexpected results. Firstly, it is not clear to what applicant is referring in Rose and secondly the claims do not recite any degree of folding or unfolding. Rose et al show that VSV glycoprotein G has been widely used as a model for integral membrane proteins and show, using this model, construction of a secreted form of the VSV glycoprotein G (page 754). Using these techniques, one would reasonably expect to express glycoprotein D as a secreted form of the HSV. The examiner notes applicant's statement concerning the time and money spent as tantamount to commercial success. It is the examiner's position that commercial success denotes that product has been marked and sold to the public and has generated a

substantial amount of income as a result of the success of the product.

The examiner notes applicant's reference to the article by Weiss et al and the expression of a chimeric glycoprotein and not a gD truncated HSV glycoprotein. As has been stated, the claims do not exclude the presence of other ingredients in the vaccine and the rejection was under 35 U.S.C. §103 not 35 U.S.C. §102. Moreover, it would still appear that the glycoprotein D disclosed in Weiss was capable of generating neutralizing antibodies.

New Grounds of Rejection

12. Claims 10-23 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 10-23 of copending application Serial Nos. 08/470,107 and 08/459,147 . This is a *provisional* double patenting rejection since the conflicting claims have not in fact been patented.

13. Claims 22 and 23 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The language of the claims is not as precise as the subject matter permits such that one may reasonably know what the metes and bounds of the claims. The claims are indefinite in the recitation of "additional effective glycoprotein" because it is unclear what applicant intends.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

14. Claims 16 and 17 are rejected under 35 U.S.C. § 103 as being unpatentable over Watson et al, 1982 in view of Rose et al, 1982 as applied to claims 10, 11, 13-15, 18 and 19 above and further in view of Kaufman et al, 1982. The claims are drawn to a method of producing a vaccine comprising a truncated membrane-free glycoprotein of herpes simplex virus comprising preparing the DNA, incorporating the DNA into an expression vector, transfecting a mammalian host cell line deficient in DHfr and collecting the secreted polypeptide. The teachings of Watson et al and Rose et al have already been described in previous office actions. Watson et al and Rose et al differ from the claimed invention in not specifically describing a DHfr deficient cell line as a selectable marker. However, Kaufman et al teach a DHfr

deficient cell used as a host such that DHfr can act as a functional marker gene (abstract and materials and methods). It is stated (page 1317) that "[t]he major advantage of the use of the system to examine gene expression is that minimal expression is required for transformation to the DHfr+ phenotype.". It is also stated that the system is exquisitely sensitive to gene expression. It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the DHfr- cell so that the vector could be constructed to contain DHfr as an easily selectable indicator of transformed cells. It would have been expected, barring evidence to the contrary, that the expression of the gene coding for the HSV glycoproteins would be efficient and the glycoprotein would be capable of generating neutralizing antibodies when administered.

15. Claims 12, 20-23 are rejected under 35 U.S.C. § 103 as being unpatentable over Watson et al, 1982 in view of Rose et al, 1982 as applied to the above claims and further in view of Chan, 1983. The claims are drawn to a vaccine comprising a truncated glycoprotein C and mixtures of glycoproteins from HSV. The teachings of Watson et al and Rose et al have already been described in previous office actions. Additionally, 'Watson et al state that it is known that antiserum to each of the glycoproteins (e.g. gA, gB and gD) can neutralize infectivity of the homologous HSV type in an <u>in vitro</u> assay. Neither Watson,

nor Rose describe immunization with a mixture of glycoproteins. However, Chan describes immunization of mice with HSV glycoproteins and challenge with HSV-1 (page 346, 348-350) and suggests that glycoproteins gC, gD or a mixture of gA and gB have been implicated in antibody dependent cellular and complement mediated cytotoxicity and that purified glycoproteins can be used in protective immunization against HSV (abstract and page 343). Thus it would have been obvious to one of ordinary skill in the art at the time the invention was made to include a mixture of glycoproteins from HSV in a vaccine composition. It would have been expected, barring evidence to the contrary, that the viral glycoproteins would be effective in generating immune responses which would be protective against HSV.

16. Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Lynette F. Smith, Art Unit 1813 and should be marked "OFFICIAL" for entry into prosecution history or "DRAFT" for consideration by the examiner without entry. The Art Unit 1813 FAX telephone number is (703)-305-7939. FAX machines will be available to receive transmissions 24 hours a day. In compliance with 1096 OG 30, the filing date accorded to each OFFICIAL fax transmission will be determined by the FAX machine's stamped date found on the last page of the transmission, unless that date is a Saturday,

Sunday or Federal Holiday with the District of Columbia, in which case the OFFICIAL date of receipt will be the next business day.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynette F. Smith whose telephone number is (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Smith/lfs LFS
July 29, 1996

L. F. Smith
LYNETTE F. SMITH
PRIMARY EXAMINER
GROUP 1800